REMARKS

The rejection under 35 USC §112, first paragraph

The examiner maintained the rejection of claims 3, 14, 17, and 19 under 35 USC §112, first paragraph, for assertedly being enabled for a polynucleotide encoding the polypeptide of SEQ ID NO: 12, but lacking enablement for a polypeptide which is at least 90% to the polypeptide of SEQ ID NO: 13, or a polynucleotide which is at least 80%, 90% or 95% identical to SEQ ID NO: 12. [Office Action at p. 2] The examiner argued that the specification does not establish

> (A) regions of the protein structure which may be modified without effecting [sic] phenylalanine ammonia lyase activity, (B) the general tolerance of phenylalanine ammonia lyase of SEQ ID NO: 12 to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any phenylalanine ammonia lyase residues with an expectation of obtaining the desired enzymatic or biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite choices is likely to be successful." [Office Action, pp. 3-4]

The examiner relied on the disclosure of Seffernick, et al. (J. Bacteriol. April 2001, p. 2405), showing two 475 amino acid proteins that are 98% identical but have different function, to purportedly support the rejection.

The applicants respectfully disagree. In response to the first Office Action in the application (*i.e.*, the response mailed December 21, 2004), the applicants demonstrated a large number of specific modifications described in the specification which the examiner acknowledged at p. 5 of the present Office Action. The applicants herein demonstrate that, at the time the present application was filed, the art included a large number of known phenylalanine ammonia lyase (PAL) polypeptide sequences from other species, and that these known sequences are homologous to the PAL polypeptide disclosed in the present application. From this knowledge that was part of the art and that which is disclosed in the present application, the worker of ordinary skill in the art would have been able to make and use polynucleotides encoding any of a large number of variants of the PAL polypeptide set out in SEQ ID NO: 13 without undue experimentation.

For example, attached hereto as Exhibit A, is a BLAST search (carried out April 18, 2005) using the PAL polypeptide of SEQ ID NO: 13 as the query sequence. As can be seen

therein, over seven pages of sequences with high homology to SEQ ID NO: 13 were obtained. The applicants acknowledge that many of these sequences identified were not known at the time the present application was filed. However, as shown in Exhibits B-X, many were known, and these 23 sequences (selected from only the first 40 shown in the BLAST results) are simply representative of the numerous PAL polypeptides shown in the seven plus pages of homologous polypeptides. From only these 23 sequences, the worker of ordinary skill would have been able to readily identify conserved PAL polypeptide regions, as well as those regions wherein modifications would be expected to have little or no affect on PAL enzymatic activity (*i.e.*, non-conserved regions wherein amino acid changes do not introduce significant secondary structural changes).

Moreover, the applicants point out that the BLAST search results in Exhibit A also include a large number of polypeptides which encode histidine ammonia lyase polypeptides which are also homologous to the polypeptide of SEQ ID NO: 13. From this homology data, the worker of ordinary skill would have been able to determine regions wherein modifications would be expected to substantially alter enzymatic activity to produce a completely different protein activity, or in the alternative, certain specific modifications to avoid if maintaining PAL activity was desired.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *United States v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988). Moreover, a patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463 (Fed. Cir. 1984). As shown above, conserved regions in PAL polypeptides were known in the art. Moreover, the relationship between PAL polypeptides and the closely related histidine ammonia lyase polypeptides were known. The combination of this knowledge in the art and the disclosure of the present specification would have taught the worker of ordinary skill in which PAL polypeptide regions changes could be introduced, and whether the changes introduced would be expected to maintain PAL activity or modify the polypeptide to encode a wholly distinct activity. From this combination, the applicant submits that making

and using the subject matter of the rejected claims would not have required undue experimentation. Accordingly, the rejection of claims 3, 14, 17, and 19 under 35 USC §112, first paragraph, may properly be withdrawn.

Conclusion

In view of the remarks herein, the applicants submit that all claims are now in condition for allowance and respectfully request notification of the same.

No fees are believed to be due in connection with this filing, however, should any fees be deemed necessary, the Commissioner is hereby authorized to charge any such fees to our Deposit Account No. 13-2855.

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Respectfully submitted,

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